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Original article

Characterization of systemic disease in primary Sjögren's syndrome: EULAR-SS Task Force recommendations for articular, cutaneous, pulmonary and renal involvements

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Abstract

Objective. To reach a European consensus on the definition and characterization of the main organ-specific extraglandular manifestations in primary SS.

Methods. The EULAR-SS Task Force Group steering committee agreed to approach SS-related systemic involvement according to the EULAR SS Disease Activity Index (ESSDAI) classification and proposed the preparation of four separate manuscripts: articular, cutaneous, pulmonary and renal ESSDAI involvement; muscular, peripheral nervous system, CNS and haematological ESSDAI involvement; organs not included in the ESSDAI classification; and lymphoproliferative disease. Currently available evidence was obtained by a systematic literature review focused on SS-related systemic features.

Results. The following information was summarized for articular, cutaneous, pulmonary and renal involvement: a clear, consensual definition of the clinical feature, a brief epidemiological description including an estimate of the prevalence reported in the main clinical series and a brief list of the key clinical and diagnostic features that could help physicians clearly identify these features. Unfortunately we found that the body of evidence relied predominantly on information retrieved from individual cases, and the scientific information provided was heterogeneous. The analysis of types of involvement was biased due to the unbalanced reporting of severe cases over non-severe cases, although the main sources of bias were the heterogeneous definitions of organ involvement (or even the lack of definition in some studies) and the heterogeneous diagnostic approach used in studies to investigate involvment of each organ.

Conclusion. The proposals included in this article are a first step to developing an optimal diagnostic approach to systemic involvement in primary SS and may pave the way for further development of evidence-based diagnostic and therapeutic guidelines.

CLINICAL SCIENCE

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Members of the EULAR SS task force are available as supplementary data, at *Rheumatology* Online.

Key words: primary Sjögren's syndrome, extraglandular features, annular erythema, vasculitis, arthritis, interstitial lung disease, bronchial disease, tubular renal acidosis, interstitial nephritis, glomerulonephritis.

Rheumatology key messages

- Systemic features clearly mark the prognosis of primary SS.
- Development of the EULAR SS disease activity index score represents a step forwards in the evaluation of SS.
- General recommendations for adequate diagnosis of joint, cutaneous, pulmonary and renal involvements in SS are included.

Introduction

Primary SS (pSS) is a heterogeneous autoimmune disease that may be expressed in many guises: the disease spectrum extends from sicca syndrome to systemic involvement (extraglandular manifestations) [1]. While sicca features affect primarily quality of life and cause local complications in the mucosa involved, systemic involvement marks the disease prognosis. SS patients may develop a large number of extraglandular manifestations, either as the presenting manifestation or during the evolution of the disease [2]. Various studies have analysed the prevalence and characteristics of systemic involvement in pSS with differing results, which may be due to the small number of patients analysed, the different sets of classification criteria used and, especially, the lack of a standardized definition of the main organ involvements [3].

The EULAR has recently promoted and supported an international collaborative study (the EULAR-SS Task Force) aimed at developing consensual disease activity indexes in SS. The project steering committee, with the formal approval of all the SS Task Force participants involved in the study, decided to develop two indexes [the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) and the EULAR SS Disease Activity Index (ESSDAI)] [4, 5]. The ESSDAI index activity included organ-by-organ definitions that were agreed on by a large number of experts in SS, thus providing a standardized instrument for the homogeneous evaluation of systemic activity in clinical trials and daily practice. The ESSDAI has high content validity since it includes definitions of the main systemic manifestations seen in the largest series of patients with pSS and stratifies the items of each domain according to severity [6].

Methods

The broad consensus obtained on the ESSDAI score provides an excellent opportunity to refine the characterization of SS-related systemic involvement using an evidence-based methodological approach according to the organ-by-organ classification used in the ESSDAI. We carried out a systematic review focused on 273 articles on SS-related systemic features reported in patients fulfilling the 2002 American–European Consensus Group (AECG) criteria (see supplementary reference list, available at *Rheumatology* Online) in order to collect currently available evidence that may pave the way for characterization (definition, prevalence, clinical characteristics and diagnostic approach) of the main organ-specific extraglandular manifestations in pSS following the ESSDAI organ-by-organ classification. This is the first article focused on the characterization of joint, cutaneous, pulmonary and renal involvement.

Results

Joint involvement

Arthralgia

Arthralgia is a symptom characterized by joint pain without inflammatory signs in the joint(s) involved. The ESSDAI score classifies the presence of arthralgia in hands, wrists, ankles and feet accompanied by morning stiffness (>30 min) as a low activity level [4]. Systematic review identified 27 studies that analysed the prevalence of joint involvement in patients with pSS (supplementary Table S1, available at *Rheumatology* Online). Joint involvement (including either arthralgia or arthritis) was reported in 2784 of 5268 (53%) patients.

Arthritis

Arthritis is the inflammation of one or more joints, characterized by joint pain, heat, redness and swelling during the physical examination. The ESSDAI score classifies the severity of arthritis according to the number of joints involved (moderate, fewer than five joints; high, more than five joints) [4]. A systematic review found that arthritis was reported in 834 of 5276 (16%) patients (Table 1). Epidemiological features were not detailed.

Arthritis was characterized in detail in 84 patients: arthritis was reported predominantly as symmetrical [60 patients (71%)], while 14 patients (17%) presented with monoarthritis. Although the number of joints involved varied, it was fewer than five in 144 of 163 (88%) patients. Three studies described the location of the arthritis (supplementary Table S2, available at *Rheumatology* Online), which was predominantly reported in the proximal IP (35%) and MCP joints (35%) and the wrists (30%). Other less frequent joint presentations were rhizomelic/Jaccoud arthropathies in five cases, RS3PE syndrome in two cases and isolated cases of sacroiliitis and cricoarytenoid arthritis.

Radiologically, SS-related arthritis was overwhelmingly classified as non-erosive, with bone erosions being found

Table 1 Main characteristics of arthritis in patients with primary SS

Feature	Patients, *n* (%)
Prevalence (*n* = 5276)	834 (16)
Female:male ratio	Not detailed
Age at diagnosis, mean, years	Not detailed
Clinical features of arthritis (*n* = 84), *n*/*N* (%)	
Symmetrical	60/84 (71)
Monoarthritis	14/84 (17)
Number of joints involved (*n* = 163)	
<5 joints involved	144 (88)
⩾5 joints involved	19 (12)
Location of arthritis (*n* = 152)	
Proximal IP joint	57 (35)
MCP joint	57 (35)
Wrist	49 (30)
Elbow	25 (15)
Knee	17 (10)
Ankle	16 (10)
Shoulder	9 (6)
MTP joint	8 (5)
Distal IP joint	5 (3)
Radiological bone erosions (*n* = 309)	15 (5)
Anti-CCP positivity (*n* = 1907)	118 (7)

Variables were not detailed in all studies and the prevalence of a specific feature is stated as the number of cases with that feature/number of cases in which the feature was detailed.

in only 15 of 309 (5%) patients; however, erosions were overwhelmingly reported in studies using musculoskeletal US or MRI. Seventeen studies tested anti-CCP in pSS and 118 of 1907 (7%) patients were positive (supplementary Table S3, available at *Rheumatology* Online).

Cutaneous involvement

Annular erythema/scLE

Annular erythema (AE) is an erythematous, photosensitive rash characterized by a wide elevated border and central pallor (annular polycyclic lesions), and is also known as scLE [7]. Lesions heal without scarring or atrophy, but may result in hypopigmentation. AE is included in the ESSDAI cutaneous domain and classified as a moderate activity level manifestation [4]; cutaneous biopsy is not mandatory.

AE was reported in 55 of 634 (9%) patients with pSS included in retrospective studies; systematic review identified 56 additional patients included in case series/reports (supplementary reference list, available at *Rheumatology* Online). AE patients had a mean age of 45 years (range 22–74 years) and a female:male ratio of 13:1 (Table 2). Fifty-two cases (47%) were reported in Asian patients (overwhelmingly Japanese). Anti-Ro/SS-A and/or anti-La/SS-B antibodies were detected in 82 of 90 (91%) patients; of the 82 immunopositive patients, 62 (76%) were positive for the two antibodies, 18 for only anti-Ro/SS-A and 2 for only anti-La/SS-B; only 8 patients had negative anti-Ro/La antibodies.

Table 2 Main characteristics of patients with primary SS presenting with annular erythema/scLE

Feature	Patients, *n* (%)
Prevalence (*n* = 634)	55 (9)
Cases reported from Asian countries (*n* = 111)	52 (47)
Female:male ratio (*n* = 57)	13:1
Age at diagnosis, years (*n* = 57)	45
Location of annular erythema lesions (*n* = 64)	
Face	39 (81)
Upper arms	22 (34)
Trunk	8 (12)
Neck	16 (25)
Lower arms	10 (16)
Hands	3 (5)
Disseminated	7 (11)
Cutaneous biopsy (*n* = 111)	51 (46)
Histopathological features (*n* = 20)	
Perivascular lymphocytic infiltration	20 (100)
Periependymal lymphocytic	12 (60)
IIF positive	4 (57)
Epidermal changes	2 (29)
Immunological profile (*n* = 90)	
Anti-Ro and/or anti-La	82 (91)
Anti-Ro	70 (78)
Anti-La	64 (71)
Negative	8 (9)
Immunological combination (*n* = 82)	
Anti-Ro + anti-La	62 (76)
Isolated anti-Ro	18 (22)
Isolated anti-La	2 (2)

Variables were not detailed in all studies and the prevalence of a specific feature is stated as the number of cases with that feature/number of cases in which the feature was detailed.

The location of AE lesions was detailed in 64 cases (Table 2), including the face in 39 (61%), the upper arms in 22 (34%) and the neck in 16 (25%) patients; lesions were less frequent in the lower arms (*n* = 10), trunk (*n* = 8) and hands (*n* = 3), and 7 patients had generalized lesions. AE was the first manifestation of pSS in 71% of patients [8]. Three clinical types of AE have been described in Japanese patients [9]: isolated doughnut-ring-like erythema with an elevated border (type I, accounting for nearly 85% of cases), scLE-like marginally scaled polycyclic erythema (type II) and papular insect bite-like erythema (type III).

Cutaneous biopsy was carried out in 51 (46%) patients. Histopathological features were detailed in only 20 patients and disclosed perivascular lymphocytic infiltration in all cases, peri-ependymal lymphocyte infiltration in 12 (60%), positive indirect immunofluorescence in 4/7 (57%) and epidermal changes in 2/7 (29%) patients (Table 2).

Table 3 Main characteristics of patients with primary SS presenting with cutaneous vasculitis

Feature	Patients, *n* (%)
Prevalence (*n* = 6301)	610 (10)
Female:male ratio (*n* = 71)	23:1
Age at diagnosis, years (*n* = 71)	53
Clinical presentation (*n* = 170)	
Cutaneous purpura	149 (88)
Cutaneous ulcers	16 (9)
Urticarial vasculitis	12 (7)
Cutaneous biopsy (*n* = 174)	80 (46)
Histopathological features (*n* = 59)	
Leucocytoclastic vasculitis	54 (90)
Lymphocytic vasculitis	1 (2)
Capillaritis	1 (2)
Microthrombosis	1 (2)
Necrotizing vasculitis	2 (4)
Immunological profile	
Anti-Ro (*n* = 87)	54 (62)
Anti-La (*n* = 86)	29 (34)
Cryoglobulins (*n* = 72)	26 (36)

Variables were not detailed in all studies and the prevalence of a specific feature is stated as the number of cases with that feature/number of cases in which the feature was detailed.

Cutaneous vasculitis

Vasculitis is the inflammation of the blood vessels. The clinical expression of vasculitis depends on the location of the vessels affected, with the skin being the organ predominantly involved. In pSS, the ESSDAI score classifies cutaneous vasculitic activity as moderate or high according to the cutaneous extension (<18% or >18% of the body surface area involved, respectively) and the presence of ulcers (high activity); cutaneous biopsy is not mandatory. Extracutaneous vasculitis, including renal and neuropathic cryoglobulinemic involvement, was included in the corresponding renal and peripheral nerve system ESSDAI domains [4].

Vasculitis was reported in 610 of 6301 (9.7%) patients with pSS. Epidemiological features were detailed in 71 cases [mean age 53 years (range 31–79), female:male ratio 23:1] (Table 3).

Patients overwhelmingly presented with cutaneous purpura [149/170 (88%)], with other cutaneous lesions such as nodules, digital lesions or maculopapular rash being rarely reported; cutaneous ulcers were reported in 14 of 170 (8%) patients. Immunological markers showed anti-Ro/SS-A in 54 of 87 (62%) patients and anti-La/SS-B in 29 of 86 (34%). Systematic review identified 12 cases of urticarial vasculitis reported in patients with pSS (Table 3).

Cryoglobulins were tested in 72 cases and were positive in 26 (36%). Vasculitis was confirmed by biopsy in 80 of 174 (46%) of reported cases; the results were detailed in 59 cases, with 54 (90%) presenting with cutaneous leucocytoclastic vasculitis.

Pulmonary involvement

Pulmonary involvement is defined by the presence of respiratory symptoms (mainly persistent cough and/or dyspnoea) associated with altered pulmonary diagnostic tests [pulmonary function tests (PFTs) and/or high-resolution CT (HRCT) scan]. A significant percentage of patients with pSS may present with chronic respiratory symptoms (mainly non-productive cough) associated with mucosal dryness of the upper respiratory tract. In fact, the ESSDAI [4] accepts active pulmonary involvement in patients presenting with persistent respiratory symptoms but normal imaging studies; in these patients, pulmonary involvement is classified as low activity. However, the ESSDAI [4] also accepts active pulmonary involvement in asymptomatic patients with altered pulmonary imaging in these cases, pulmonary involvement is also classified as low activity. Moderate or severe pulmonary disease activity was graded in the ESSDAI according to PFT results [moderate if the PFTs are abnormal, severe if the PFTs disclose a lung diffusing capacity for carbon monoxide (DLCO) <40% and/or a forced vital capacity (FVC) <60%] and the functional class of patients with HRCT-proven interstitial lung disease (ILD) [moderate in patients with New York Heart Association (NHYA) class II and severe in patients with NHYA classes III and IV] [4]. Pulmonary biopsy is not mandatory.

Systematic review identified three main groups of patients in whom pulmonary involvement was investigated: unselected SS patients, patients with suspected lung involvement and patients with lung involvement confirmed by HRCT and/or lung biopsy. Overall analysis of studies including unselected SS patients found pulmonary involvement in 795 of 4897 (16%) patients, including both bronchial and parenchymal involvement; one study focused on bronchial involvement and found bronchiectasis in 41 of 507 (8%) patients [10]. Epidemiological features were detailed in 425 cases, with a mean age of 58.4 years and a female:male ratio of 6:1 (Table 4).

Clinical features were detailed in 206 patients and included dyspnoea in 129 (62%), cough in 112 (54%), sputum/rales in 29 (14%), chest pain in 11 (5%) and fever in 7 (2%) (Table 4). The immunological profile showed that 186 of 252 (74%) patients had positive anti-Ro/SS-A antibodies and 82 of 234 (35%) had anti-La/SS-B antibodies. Isolated reports of infrequent pulmonary involvement in pSS included isolated cases of pulmonary haemorrhage, pulmonary veno-occlusive disease, alveolar proteinosis and shrinking lung syndrome.

PFT results were detailed in 16 studies including 330 patients with pSS and were reported as altered in 212 (64%); specific results were detailed in 163 patients, showing a restrictive pattern in 104 (64%) patients and an obstructive pattern in 34 (21%). Table 4 summarizes the CT findings of 526 patients included in 17 studies, with bronchiectasis/bronchiolar abnormalities (50%) and ground glass opacities/interstitial changes (49%) being the most frequent abnormalities. Histopathological diagnoses were detailed in 146 patients (Table 4), with non-specific interstitial pneumonia [66 cases (45%)],

Table 4 Main characteristics of patients with primary SS presenting with pulmonary involvement

Feature	Patients, *n* (%)
Prevalence ($n = 4897$)	795 (16)
Female:male ratio ($n = 425$)	6:1
Age at diagnosis, years ($n = 425$)	58
Clinical features ($n = 260$)	
Dyspnoea	129 (62)
Cough	112 (54)
Sputum/rales	29 (14)
Chest pain	11 (5)
Fever	7 (2)
Altered pulmonary function test results ($n = 163$)	
Restrictive pattern	104 (64)
Obstructive pattern	34 (21)
Other results	25 (15)
High-resolution CT findings ($n = 146$)	
Bronchiectasis/bronchiolectasis/ bronchiolar abnormalities	262 (50)
Ground glass opacities/interstitial changes	257 (49)
Small or large nodules	122 (23)
Interlobular septal thickening	119 (23)
Reticular opacities/pattern	117 (22)
Cysts/bullae	115 (22)
Airspace consolidation	73 (14)
Honeycomb	71 (13)
Non-septal linear/plate-like opacities	65 (12)
Mosaic perfusion/attenuation	35 (7)
Thickening of bronchovascular bundles/tree in bud opacities	29 (6)
Emphysema/air trapping	27 (5)
Pleural thickening/effusion	26 (5)
Histopathological findings ($n = 526$)	
Non-specific interstitial pneumonia	66 (45)
Bronchiolitis	36 (25)
Usual interstitial pneumonia	24 (16)
Lymphocytic interstitial pneumonia	22 (15)
Organizing pneumonia	11 (7)
Amyloidosis	9 (6)
Lymphoma	6 (4)
Non-caseating granuloma	4 (3)
Neutrophilic pneumonia[a]	4 (3)
Cystic disease	2 (1)
Atelectatic fibrosis[a]	2 (1)
Interstitial lung disease[a]	2 (1)
Honeycomb changes[a]	1 (0.7)
Immunological profile	
Anti-Ro ($n = 252$)	186 (74)
Anti-La ($n = 234$)	82 (35)

[a]Incomplete histopathological description. Variables were not detailed in all studies, and the prevalence of a specific feature is stated as the number of cases with that feature/number of cases in which the feature was detailed. HRCT: high-resolution CT.

bronchiolitis [36 cases (25%)], usual interstitial pneumonia [24 cases (16%)] and lymphocytic interstitial pneumonia [22 cases (15%)] being the most frequent diagnoses. Enomoto *et al*. [11] reported a ratio of fibrotic:cellular non-specific interstitial pneumonia of 19:3.

Renal involvement

Tubulointerstitial involvement

Chronic tubulointerstitial nephritis is the main renal involvement associated with pSS; renal tubular acidosis (RTA) is the principal clinical presentation and is caused by generalized dysfunction of the renal tubules leading to renal acid retention or bicarbonate loss. There are three major forms of RTA: types I and IV distal RTA and proximal RTA (type II). Type I RTA is diagnosed with the finding of a persistent urine pH $>$ 5.3 even in the presence of a metabolic acidosis induced by ammonium chloride loading, while type II RTA is defined as a urine pH $>$ 7.5 and the appearance of $>$15% of the filtered bicarbonate in the urine when the serum bicarbonate concentration is raised to a normal level [12]. Some patients may have an incomplete variant of the disease and retain normal serum bicarbonate levels despite alkaline urine pH [12]. The ESSDAI score classifies disease activity in patients with RTA as low or moderate according to the absence or presence of renal failure [glomerular filtration rate (GFR) $\geqslant$60 or $<$60 ml/min, respectively] [4]. Renal biopsy is not mandatory.

Renal tubular acidosis was diagnosed in 186 of 2005 (9%) unselected patients with pSS. RTA types were specified in 321 cases: 313 (97%) were classified as distal RTA and 8 (3%) as proximal (Fanconi syndrome). Epidemiological features were detailed in 208 cases, with a mean age of 41.2 years (range 15–84) and a female:male ratio of 27:1 (Table 5).

The clinical presentation was detailed in 198 cases (Table 5). RTA was diagnosed from clinical features in 130 (66%) cases and laboratory findings (mainly mild renal failure and/or proteinuria) in the remaining 68 (34%) cases. Of symptomatic patients, 90 (69%) presented with hypokalaemic weakness/paralysis (9 with respiratory failure), 23 (12%) with renal colic, 33 (17%) with radiological nephrocalcinosis, 26 (13%) with osteomalacia (10 with pathological fractures) and 7 (4%) with polyuria/polydipsia (diabetes insipidus). Renal failure (creatinine $>$1.2 mg/dl) was reported in 47 (24%) patients. Immunological markers showed anti-Ro/SS-A in 160 of 225 (71%) patients and anti-La/SS-B in 116 of 215 (54%).

Renal biopsy was carried out in 149 of 321 (46%) patients with RTA, of which 140 (94%) disclosed tubulointerstitial nephritis. In addition, some patients with pSS may present with biopsy-proven tubulointerstitial nephritis but with no evidence of tubular acidosis [13].

Glomerular involvement

GN is an acute or chronic inflammation of the glomeruli, demonstrated by renal biopsy, which often comes to light when routine analyses are abnormal (proteinuria, renal failure). The ESSDAI score classifies disease activity in patients with GN as low, moderate or high according to the level of 24 h proteinuria ($<$1, 1–1.5 and $>$1.5 g/day,

TABLE 5 Main characteristics (renal tubular acidosis and GN) of patients with primary SS presenting with renal involvement

Feature	Patients, *n* (%)
Renal tubular acidosis	
Prevalence (*n* = 2005)	186 (9)
Female:male ratio (*n* = 208)	27:1
Age at diagnosis, years (*n* = 208)	41
RTA classification (*n* = 321)	
Type I (distal RTA)	313 (97)
Type II (proximal RTA/Fanconi syndrome)	8 (3)
Symptomatic presentation (*n* = 130)	
Hypokalaemic weakness/paralysis	90 (69)
Renal colics	23 (12)
Radiological nephrocalcinosis	33 (17)
Osteomalacia	26 (13)
Polyuria/polydipsia	7 (4)
Renal failure (creatinine >1.3 mg/dl) (*n* = 198)	47 (24)
Renal biopsy (*n* = 321)	149 (46)
Histopathological features (*n* = 149)	
Interstitial nephritis	140 (94)
Other features	9 (6)
Immunological profile	
Anti-Ro (*n* = 225)	160 (71)
Anti-La (*n* = 215)	116 (54)
GN	
Prevalence (*n* = 2005)	78 (4)
Female:male ratio (*n* = 81)	19:1
Age at diagnosis, years (*n* = 81)	53
Clinical presentation (*n* = 76)	
Oedema/nephrotic syndrome	23 (22)
Laboratory abnormalities	43 (78)
Laboratory abnormalities	
Renal failure (creatinine >1.3 mg/dL) (*n* = 72)	36 (50)
24 h proteinuria >0.5 g (*n* = 36)	
0.5–1 g	4 (11)
1–1.5 g	7 (19.5)
>1.5 g	25 (69.5)
Haematuria (*n* = 68)	35 (51)
Renal biopsy (*n* = 321)	149 (46)
Histopathological features (*n* = 149)	
Membranoproliferative GN	47 (38)
Mesangial proliferative GN	29 (23)
Membranous glomerulonephritis	28 (22)
Focal segmental glomerulonephritis	21 (17)
Crescentic rapidly progressive GN	9 (7)
IgA nephropathy	7 (6)
Glomeruloesclerosis	2 (2)
Minimal change nephropathy	2 (2)
Thin basement membrane nephropathy	1 (1)
GN not specified	3 (2)
Immunological profile	
Anti-Ro (*n* = 65)	47 (72)
Anti-La (*n* = 65)	29 (45)
Cryoglobulins (*n* = 56)	29 (52)
ANCA (*n* = 16)	8 (50)

Variables were not detailed in all studies and the prevalence of a specific feature is stated as the number of cases with that feature/number of cases in which the feature was detailed. RTA: renal tubular acidosis.

respectively). The following features classify ESSDAI renal activity as high: haematuria, renal failure (GFR <60 ml/min) and proliferative GN/cryoglobulinaemia [4].

GN was diagnosed in 78/2005 (4%) unselected patients with pSS. Systemic review identified 149 cases of biopsy-proven GN (supplementary reference list, available at *Rheumatology* Online). Epidemiological features were detailed in 81 patients, with a mean age of 53 years (range 25–86) and a female:male ratio of 19:1.

The clinical presentation was detailed in 76 cases, of whom 23 (22%) presented with oedema/nephrotic syndrome (Table 5). Renal function was detailed in 72 cases and showed renal failure (creatinine >1.3 mg/dl) in 36 (50%); creatinine >2 mg/dl was reported in 13 (12%) patients (only 3 had values >5 mg/dl). Twenty-four hour proteinuria was detailed in 52 patients, of whom 16 (31%) had a level <0.5 g. Of the 36 patients with proteinuria >0.5 g, 4 (11%) had 0.5–1 g (low ESSDAI activity), 7 (19.5%) had 1–1.5 g (moderate ESSDAI activity) and 25 (69.5%) had >1.5 g (high ESSDAI activity); haematuria was reported in 35/68 (51%) cases. Immunological markers showed anti-Ro/SS-A in 47/65 (72%) patients and anti-La/SS-B in 29/65 (45%).

Cryoglobulins were tested in 56 patients and were positive in 29 (52%), while ANCA was tested in 16 and was positive in 8 (7 pANCA, 1 cANCA) (Table 5). The results of renal biopsy (Table 5) disclosed mainly membranoproliferative (*n* = 47), proliferative (*n* = 29) and membranous (*n* = 28) GN. A recent study [14] found high rates of adverse outcomes in patients with clinically overt, biopsy-proven renal involvement, especially in those with cryoglobulinemic-mediated glomerular damage. Two of the seven cases of IgA nephropathy in patients with pSS had associated amicrobial pustulosis [15, 16].

Discussion

The clinical study of pSS has traditionally been based on a diagnostic approach predominantly focused on glandular involvement, even though pSS is undeniably more than a sicca disease. In our systematic review we followed the 2002 classification criteria for the diagnosis of pSS, a set of criteria that excludes patients with other associated systemic diseases (principally SLE, RA and SSc). Despite the fact that a long list of extraglandular features involving the majority of organs and systems has been reported in the last 30 years, few studies have attempted to characterize and detail how systemic involvement should be defined [17–19]. Therefore the need for a consensus on a homogeneous diagnostic approach to systemic involvement in pSS is clear. We believe that a systematic review of the current scientific evidence could pave the way to the building of this consensus. Unfortunately the body of evidence relied predominantly on information retrieved from individual cases, either reported in isolation or included in case series [197/278 studies evaluated (71%)]. In addition, the scientific information provided was heterogeneous, and we identified a

Table 6 General recommendations for an adequate description of systemic involvement in primary SS (articular, cutaneous, pulmonary and renal involvements)

Definition of organ-specific systemic involvement
The organ involvement should be clearly defined together with the main symptoms and the results of diagnostic tests.
The inclusion of asymptomatic patients with altered diagnostic tests in pulmonary and renal involvements should be clearly stated.
Detailing clinical presentation
For systemic presentations reported very infrequently in primary SS, we recommend to search for other associated systemic diseases, especially in patients with:
Erosive arthritis
Infrequent location of arthritis
Extracutaneous non-cryoglobulinaemic vasculitis
Proximal RTA
Always use standardized, consensual international definitions for the organ involvement: erosive arthritis, vasculitis, ILD, RTA and glomerulonephritis.
Autoantibodies studies
Specific autoantibodies related to other systemic autoimmune diseases in which organ-specific involvements overlap should be provided.
Negativity should confirm primary SS in patients presenting with:
Arthritis (SLE, RA)
AE (SLE)
Cutaneous vasculitis (ANCA vasculitides)
ILD (SSc)
GN (SLE, vasculitis).
Histopathological studies
Requirement for histopathological studies is highly recommended in some SS-related involvements (extracutaneous vasculitis, GN). It does not seem to be essential for diagnosis in other types of involvement (AE, cutaneous purpura, RTA).

AE: annular erythema; RTA: renal tubular acidosis; ILD: interstitial lung disease.

significant number and types of biases (supplementary Table S4, available at *Rheumatology* Online), of which the most frequent were publication and detection biases, although most publication biases had little influence (low degree). The analysis of involvements was also biased due to the unbalanced reporting of severe cases over non-severe cases (cutaneous ulcers in vasculitic involvement, symptomatic RTA in renal involvement). However, the main sources of bias were the heterogeneous definitions of organ involvement (or even the lack of definition in some studies) and the heterogeneous diagnostic approach used in studies to investigate each organ involvement.

In spite of the biases detected, the overall analysis of the reported cases for each involvement (accepting the low level of current evidence) has shed some light on the definitions of systemic involvement, and some general recommendations for the description of systemic involvement in pSS may be proposed (Table 6). In addition, the following specific recommendations for reporting articular, cutaneous, pulmonary and renal involvements in studies including patients with pSS were agreed upon.

Recommendations for articular involvement

Patients may report arthralgia (subjective feeling) and arthritis (joint inflammation that should be confirmed clinically by physical examination), but the two features should be detailed separately. A description of SS-related arthritis should include the number and location of joints involved, the arthritis pattern (symmetrical, additive) and the results of radiological studies, including the number of patients evaluated (and the reason for evaluation) and the techniques used (X-ray, US, MRI); erosive arthritis should be defined according to EULAR recommendations [20]. Patients presenting with atypical or severe arthritis (more than five joints involved, location other than the hands or erosive arthritis) should be investigated more specifically, with investigation of associated RA (anti-CCP antibodies, musculoskeletal US and/or MRI). Patients with pSS may present with arthritis, although this should be considered as related to RA in patients presenting with erosive arthritis and/or positive anti-CCP antibodies (SS associated with RA); although anti-CCP antibodies has been reported in 7% of patients classified as pSS, a significant percentage of these patients will develop typical erosions of RA and will be classified as RA + SS.

Recommendations for cutaneous involvement

The ESSDAI includes several non-sicca cutaneous features including AE/SCLE, purpura, cutaneous vasculitis, urticarial vasculitis and erythema multiforme [21]; all these features should be detailed separately, together with other non-ESSDAI cutaneous features, taking into account the fact that some patients [8] may present different involvements at different times; the location and types of lesions should be clearly detailed. AE should be diagnosed clinically and overwhelmingly suspected in Ro/La-positive patients presenting with photosensitive annular polycyclic lesions; in these patients, underlying SLE

should always be ruled out by testing for dsDNA autoantibodies. Vasculitis should also be diagnosed clinically and overwhelmingly suspected in patients presenting with cutaneous purpura/ulcers. Cutaneous biopsy is not mandatory but is recommended principally to rule out other processes in patients presenting with atypical lesions or those with suspected systemic vasculitides. In patients with cutaneous vasculitis, testing for hypergammaglobulinaemia and cryoglobulins is mandatory, while testing for ANCA may be reserved for cases in which cryoglobulinaemia is ruled out and/or systemic vasculitis is suspected. The current vasculitis nomenclature proposed by the 2012 Revised International Chapel Hill Conference should be used [22].

Recommendations for pulmonary involvement

The ESSDAI includes symptomatic patients with altered diagnostic tests (PFT, HCRT or both), but also asymptomatic patients with altered tests, and symptomatic patients with normal tests; all these subsets should be clearly detailed. Smoking (past or current), drugs and other environmental factors involved in pulmonary damage should always be considered as exclusion criteria. The description of patients with pulmonary involvement should detail respiratory symptoms, functional status according to the NHYA classification [23] and the number of patients evaluated by functional (PFT) and imaging (HRCT) studies. PFT results should be detailed, including at least FVC, forced expiratory volume (FEV1)/FVC and DLCO results, functional patterns (obstructive, restrictive or mixed) and the range of severity of PFT parameters according to ESSDAI definitions. A detailed description of HCRT findings should be provided, including information on how many patients have an interstitial pattern, bronchial/bronchiolar pattern or mixed pattern. Pulmonary biopsy is not mandatory but may be recommended mainly in patients with an atypical presentation or HRCT patterns or in patients with suspected overlapping systemic diseases; histopathological ILD diagnoses should be detailed according to the 2013 international multidisciplinary classification of idiopathic interstitial pneumonias [24].

Recommendations for renal involvement

The ESSDAI includes asymptomatic patients with altered renal function/urinalysis suggesting tubular acidosis or GN, but also patients with biopsy-proven interstitial nephritis or GN; all these subsets should be clearly detailed. Detailed clinical presentation should follow the rules proposed by Chadban and Atkins [25], including all symptoms related to renal involvement (oedema, nephrotic/nephritic syndrome, bone pain, muscular weakness, pseudofractures, polyuria and polydipsia). Laboratory tests should include urinalysis (red blood cells or red cell casts suggesting possible glomerular damage, white blood cells suggesting inflammation and increased protein suggesting nephron damage), serum creatinine, electrolytes and GFR. Abdominal X-ray/renal US is recommended to identify nephrocalcinosis/obstructive uropathies and, when the patient has nephrolithiasis, 24 h urinary calcium should be measured. In patients with suspected GN, testing for cryoglobulins is mandatory [26], while testing for ANCA may be reserved for patients in whom cryoglobulinaemia is ruled out and/or those in whom systemic vasculitis is suspected. A kidney biopsy is not necessary to confirm the diagnosis of RTA, but may be recommended to rule out other processes, such as IgG4-related disease [27]. However, due to the wide spectrum of histopathological scenarios seen in pSS, a kidney biopsy is highly recommended to confirm the type of GN and rule out other associated processes (mainly SLE and vasculitides, but also non-autoimmune processes); histopathological results should be detailed according to the standard definitions of glomerular diseases [25].

Conclusion

The proposals included in this article are a first step to developing an optimal diagnostic approach to systemic involvement in pSS and may pave the way for further development of evidence-based diagnostic and therapeutic guidelines. However, the overall low level of scientific evidence suggests that a degree of caution is necessary and underlines the need for further changes in the evaluation of patients with pSS, who may present a wide range of organ and system involvement, some of which are life threatening. A greater understanding of the aetiopathogenesis of extraglandular damage, active international collaborations promoting multicentre registries to enrol and characterize large cohorts of patients with pSS and international agreements on clinical, diagnostic and therapeutic guidelines may help to improve the prognosis of patients with pSS presenting with systemic involvement.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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